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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/629,074	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-12,17-19,21-23,25-27,29-33 and 38-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-8, 17-19, 21-23, 25, 29, 31, 44, 45, 48-53, 56-59, and 62* is/are rejected.

7)☒ Claim(s) *4,9,11,12,26,27,30,32,33,38-43,46,47,54,55,60 and 61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed November 24, 2003 has been entered. Claims 1, 19, and 22 have been amended. Claims 5, 28, 36, and 37 have been cancelled. Claims 44-62 have been newly added.

Accordingly, Claims 1-4, 6-12, 17-19, 21-23, 25-27, 29-33, and 38-62 are pending in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amd.

Claims 1-3, [illegible], 6, 17-19, 21, 22, and 25 stand rejected and Claims 44, 45, 48-53, 56-59, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO95/24473 (Hu et al.).

The claims are directed to a method for enhancing bone density or formation by administering to at least one first cell within a bone or within a tissue immediately surrounding a bone an adenoviral vector comprising at least one first nucleic acid encoding a vascular endothelial growth factor, such that the first nucleic acid is expressed in the cell to produce the vascular endothelial growth factor, whereby bone density or formation is enhanced within the region. Claim 18 specifically provides for the embodiment where the first nucleic acid and the second nucleic acid are the same nucleic acid. Claim 19 is directed to an adenoviral vector comprising at least one first nucleic acid encoding a vascular endothelial growth factor and at least one second nucleic acid encoding at least one osteogenic protein. However, given the language of Claim 18 the second nucleic acid referred to in Claim 19 may encode VEGF as well. Claim 22 is directed to a bone graft comprising at least one first cell having at least one first exogenous nucleic

acid encoding a vascular endothelial growth factor and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein. As discussed above, the second nucleic acid referred to in Claim 22 need not encode a distinct protein, but may also encode VEGF. Claims 44, 45, and 48-51 are directed to a method for enhancing bone density or formation by administering to at least one first cell within a bone or within a tissue immediately surrounding a bone an adenoviral vector comprising at least one first nucleic acid encoding a vascular endothelial growth factor, such that the first nucleic acid is expressed in the cell to produce the vascular endothelial growth factor, and administering to at least one second cell, within the bone or within a tissue immediately surrounding the bone, an adenoviral vector comprising at least one second nucleic acid encoding at least one osteogenic protein, such that the second nucleic acid is expressed in the cell to produce the osteogenic protein, whereby bone density or formation is enhanced within the region.

Hu et al. discloses a polynucleotide encoding VEGF2. The reference further describes using the disclosed polynucleotide encoding VEGF2 "to promote growth of damaged bone and tissue" (page 4, paragraph 3). At page 17, paragraph 2, the reference discloses that VEGF2 may be used to induce the growth of damaged bone. Moreover, the reference specifically mentions using adenovirus to deliver a polynucleotide encoding VEGF2 (page 18, paragraphs 3-5). It discloses that cells may be transduced with the polynucleotide *ex vivo* (as recited in Claim 3 of the instant application) or *in vivo* (as recited in Claim 2 of the instant application). Claim 21 of Hu et al. is directed to treating a patient in need of VEGF2 by administering DNA encoding VEGF2. Hu et al. further discloses that VEGF has four different forms of 121, 165, 189, and 206 amino acids due to alternative splicing (page 2, paragraph 3). The reference discloses that VEGF121 and VEGF165 are soluble and promote angiogenesis (page 2, paragraph 3) As early as 1992 it was known that VEGF is responsible for persistent microvascular hyperpermeability to plasma proteins, a characteristic of normal wound healing (page 3, paragraph 2). Thus, VEGF was known to be an important factor in wound healing.

Given that various VEGFs were known in the art and that these all were known to have similar properties, as discussed by Hu et al., and further given that Hu et al. specifically disclosed that one form of VEGF, VEGF2, is useful for promoting growth of damaged bone, the skilled artisan would have been motivated to use other VEGFs and polynucleotides encoding other VEGFs to promote growth of damaged bone. A reasonable expectation of success would have been anticipated because the various VEGFs known in the art were known to have similar biological properties, as discussed by Hu et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 10, paragraph 2 of the response, Applicants assert that the '473 PCT application does not disclose or suggest the use of any of the vascular endothelial growth factors recited in amended Claims 1, 19, or 22. On the contrary, for the reasons detailed above, the reference does suggest the use of vascular endothelial growth factors other than VEGF2. Applicants further assert that the reference does not disclose or suggest any of the osteogenic proteins recited in Claims 44, 52, and 58. However, for the reasons discussed in the previous Office Action (mailed 8/19/03), given that the claims explicitly recite that the first and second nucleic acid are the same, the claims are construed to include the use of any VEGF as the osteogenic protein. Thus, the claimed invention is disclosed by Hu et al.

Claims 1-3, 6, 17-19, 21, 22, and 25 stand rejected and Claims 44, 45, 48-53, 56-59, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,935,820 (Hu et al.).

Hu et al. discloses a polynucleotide encoding VEGF2. The reference further describes using the disclosed polynucleotide encoding VEGF2 "to promote growth of damaged bone and tissue" (Column 2, lines 38-42). At Column 9, lines 57-58, the reference discloses that VEGF2 may be used to induce the growth of damaged bone. Moreover, the reference specifically mentions using adenovirus to deliver a polynucleotide encoding VEGF2 (Column 10, lines 34-55). It discloses that cells may be transduced with

the polynucleotide *ex vivo* (as recited in Claim 3 of the instant application) or *in vivo* (as recited in Claim 2 of the instant application). Hu et al. further discloses that VEGF has four different forms of 121, 165, 189, and 206 amino acids due to alternative splicing (column 1, lines 52-56). The reference discloses that VEGF121 and VEGF165 are soluble and promote angiogenesis (column 1, lines 53-55) As early as 1992 it was known that VEGF is responsible for persistent microvascular hyperpermeability to plasma proteins, a characteristic of normal wound healing (column 2, lines 8-14). Thus, VEGF was known to be an important factor in wound healing.

Given that various VEGFs were known in the art and that these were known to have similar properties, as discussed by Hu et al., and further given that Hu et al. specifically disclosed that one form of VEGF, VEGF2, is useful for promoting growth of damaged bone, the skilled artisan would have been motivated to use other VEGFs and polynucleotides encoding other VEGFs to promote growth of damaged bone. A reasonable expectation of success would have been anticipated because the various VEGFs known in the art were known to have similar biological properties, as discussed by Hu et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 10, paragraph 2 of the response, Applicants assert that the '820 patent does not disclose or suggest the use of any of the vascular endothelial growth factors recited in amended Claims 1, 19, or 22. On the contrary, for the reasons detailed above, the reference does suggest the use of vascular endothelial growth factors other than VEGF2. Applicants further assert that the reference does not disclose or suggest any of the osteogenic proteins recited in Claims 44, 52, and 58. However, for the reasons discussed in the previous Office Action (mailed 8/19/03), given that the claims explicitly recite that the first and second nucleic acid are the same, the claims are construed to include the use of any VEGF as the osteogenic protein. Thus, the claimed invention is disclosed by Hu et al.

Claims 1, 3, 6-8, 17, 18, 22, 23, 25, 29, 44, 45, 48-53, 56-59, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,398,816 (Breitbart et al., filed September 4, 1997) and U.S. Patent No. 5,935,820 (Hu et al.).

Breitbart et al. disclose the use of genetically engineered cells expressing a number of specific bioactive molecules for bone repair. The claims specifically recite that "the cells are applied to or incorporated into a prosthesis for repair or replacement of bone, cartilage, or connective tissue" (see Claim 1). The claims further recite that the cells are genetically engineered to express an effective amount of growth factors "selected from the group consisting of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (FGF), insulin-like growth factor (IGF), endothelial derived growth supplement (EDGS), keratinocyte growth factor (KCF), osteogenin, skeletal growth factor (SGF), osteoblast-derived (BDGFs), retinoids, growth hormone (GH), bone morphogenic proteins (BMPs), and transferrin" (see Claim 5). Claim 9 is specifically directed to periosteal cells genetically engineered to express BMP-7. The specification discloses that genetically engineered periosteal cells are to be used for repair of bone (see abstract at lines 6-8). The specification further discloses that cells can be implanted directly into a defect in an amount effective to promote repair (Column 8, lines 38-39). The specification makes it clear that the invention covers cells transfected with more than one of the genes mentioned in the claims. For example, at Column 3, lines 41-43, the specification states that "for repair of bone, a gene **(or genes)** encoding bone morphogenic protein is transfected into periosteal cells." Furthermore, the claims recite "bioactive molecules" in the plural form. The specification discloses using adenoviral vectors to transduce the cells (Column 8, lines 8-10).

Hu et al. discloses that VEGF has four different forms of 121, 165, 189, and 206 amino acids due to alternative splicing (column 1, lines 52-56). The reference discloses that VEGF121 and VEGF165 are soluble and promote angiogenesis (column 1, lines 53-55) As early as 1992 it was known that VEGF is

responsible for persistent microvascular hyperpermeability to plasma proteins, a characteristic of normal wound healing (column 2, lines 8-14). Thus, VEGF was known to be an important factor in wound healing. Hu et al. further discloses a polynucleotide encoding VEGF2. The reference describes using the disclosed polynucleotide encoding VEGF2 "to promote growth of damaged bone and tissue" (Column 2, lines 38-42). At Column 9, lines 57-58, the reference discloses that VEGF2 may be used to induce the growth of damaged bone. Moreover, the reference specifically mentions using adenovirus to deliver a polynucleotide encoding VEGF2 (Column 10, lines 34-55). It discloses that cells may be transduced with the polynucleotide *ex vivo* (as recited in Claim 3 of the instant application) or *in vivo* (as recited in Claim 2 of the instant application).

Given that Breitbart et al. disclose the use of genetically engineered cells expressing a number of specific bioactive molecules for bone repair and specifically points to using cells genetically engineered to express any VEGF, and further given that various VEGFs were known in the art, including VEGF121, VEGF165, VEGF189, and VEGF206, as evidenced by Hu et al., and further given that these were known to have similar properties, as discussed by Hu et al., and further given that Hu et al. specifically disclosed that one form of VEGF, VEGF2, is useful for promoting growth of damaged bone, the skilled artisan would have been motivated to use other VEGFs and polynucleotides encoding other VEGFs to promote growth of damaged bone. A reasonable expectation of success would have been anticipated because the various VEGFs known in the art were known to have similar biological properties, as discussed by Hu et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 10, paragraph 3 of the response, Applicants argue that the '816 patent does not disclose or suggest an adenoviral vector encoding any of the VEGFs recited in amended claims 1, 19, and 22. First, it is noted that the 102(e) rejection based on Breitbart et al. was not applied to Claim 19. However,

in view of the claim amendments which now recite the use of specific VEGFs and excludes the use of VEGF2 in Claims 1, 3, 6-8, 17, 18, 22, 23, 25, and 29, the rejection is set forth under 35 U.S.C. 103(a). Applicants argue that the '816 patent discloses using VEGF nucleic acids exclusively for treating skin or wounds, and not to enhance bone density or formation. Applicants point to column 6, lines 33-34 as distinguishing other bioactive molecules as bone growth factors. Contrary to Applicants assertions, Claim 1 specifically recites using the genetically engineered cells such that "the cells are applied to or incorporated into a prosthesis for repair or replacement of bone, cartilage, or connective tissue." Claim 5 specifically recites the growth factors that should be used to achieve this effect, including VEGF. None of the claims are limited to using VEGF for treating skin or wounds. Furthermore, contrary to Applicants assertions, Breitbart et al. does disclose using adenovirus to transfect the cells (column 8, lines 8-10).

Claims 1, 2, 6-8, 10, 17, and 18 stand rejected and Claims 44, 45, 48-53, 56-59, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,525,030 (Eriksson, filed December 15, 1997) and U.S. Patent No. 6,475,480 (Mehtali et al., filed July 6, 1999).

Eriksson discloses a method for stimulating bone growth by repeatedly injecting expressible genetic material encoding a product that modulates bone growth into periosteal cells (see especially Claim 3). The specification discloses that a preferred gene for delivery can include a gene that encodes a product that can modulate bone growth, which products can include cytokines and those listed in Table 3 (Column 16, line 66 to Column 18). Many of the genes listed in Table 3 are also recited in Claim 2. Furthermore, it is noted that Claim 2 recites "and a combination of any of the foregoing." Such combinations would meet the limitations of the instant claims when VEGF is included. The specification specifically states that a plurality of genes may be delivered in combination (Column 18, lines 4-5).

Mehtali et al. disclose an adenoviral vector which provides for improved expression of its cargo gene. The reference discloses a method for improving the expression and/or persistence of expression of a gene of interest in a mammal (see especially Claim 18).

Given that Eriksson discloses a method for stimulating bone growth by administering a gene to a periosteal cell and further given that Mehtali et al. discloses a method for improving the expression of a gene of interest in a mammal by using a specific type of adenoviral vector, one of skill in the art would have been motivated to employ the use of the adenoviral vector of Mehtali et al. in the method of Eriksson to boost the expression of the gene that will stimulate bone growth. Given that only standard molecular biology techniques are required to prepare an adenoviral vector as taught by Mehtali et al. carrying any gene of interest, one of skill in the art would have anticipated a reasonable expectation of success for making the necessary adenoviral vectors and using them in the method disclosed by Eriksson.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 11, paragraph 6 of the response, Applicants argue that one of skill in the art would not have been motivated to combine the disclosures because then one of ordinary skill in the art would have to disregard the teachings of the '030 patent "against the use of viral delivery of genetic material." Applicants point to column 7, lines 47-49 of the '030 patent which states that the disclosed gene delivery method "is useful for delivery of a suspension of genetic material alone, without delivery of infectious viral material ..." However, the cited passage goes on to state that the method is useful "without delivery of infectious viral material or attachment to microparticles. This is desirable because of the minimal sample preparation time required." The reference does not in any way suggest that it is preferable to use genetic material alone, in the absence of viral vectors, for any reason other than for simplifying the process. Therefore, while the disclosed method **can** be used without viral vectors, there is nothing to suggest that it is always preferable to avoid the use of viral vectors. On the contrary, the cited reference

of Mehtali et al. provides ample reason for using an adenoviral vector, i.e. to obtain increased expression of the cargo gene. For obvious reasons, researchers are always willing to go to additional effort and take additional time to achieve superior results.

Allowable Subject Matter

Claims 4, 9, 11, 12, 26, 27, 30, 32, 33, 38-43, 46, 47, 54, 55, 60, and 61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER